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Cancer Associated Macrophage Like-Cells Predict Aggressive Disease in Local and Metastatic Prostate Cancers

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ABSTRACT

Prostate cancers (PC) are intrinsically complex, with few prognostic biomarkers that differentiate between aggressive and indolent disease. Cancer associated macrophage-like cells (CAMLs) have shown to be a significant independent prognostic for poor survival in solid tumors if engorged to ≥50µm in size. However, no group has examined CAMLs in PC. In this prospective pilot study, we analyzed PSA and ≥50µm CAML presence in (n=50) Stage I-III & (n=42) metastatic PC (mPC) prior to the start of new treatment to examine the relationship between CAMLs and patient outcomes. We found that ≥50µm CAML presence significantly predicted worse patient survival in mPC, and non-significantly trended in non-metastatic disease. These preliminary results suggest that CAMLs may serve as a non-invasive prognostic biomarker that predicts for worse outcomes in both local and mPC prior to new therapies.

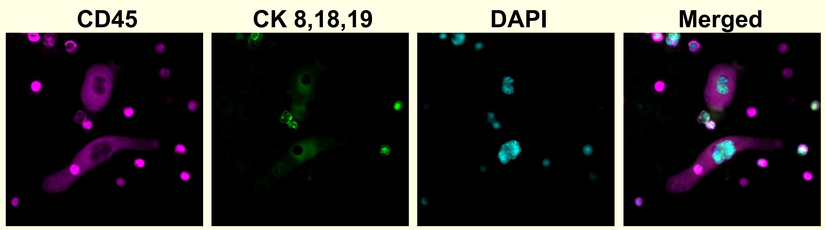


Figure 1. Two CAMLs from a metastatic prostate cancer patient. CAMLs are CD45/CD14 positive (purple) and diffuse for Cytokeratin (green).

INTRODUCTION

PC is the second most common malignancy in men globally; it is predicted that 1 of 6 men will develop PC at some point during their lifetime[1]. Given the complex heterogeneity of PC tumors, most biomarkers have failed to predict aggressive malignancies in the localized disease setting[2]. CAMLs have shown to be a non-invasive prognostic biomarker in a variety of cancers[3], with phagocytic engorgement predicting for progression and death[4].

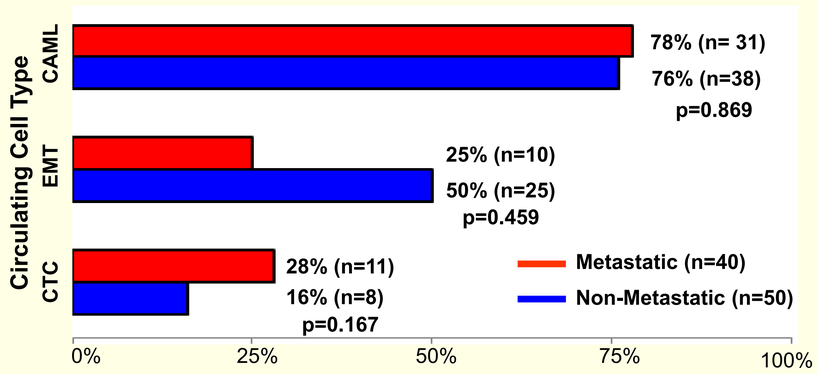
Figure 2. Patient demographic table

Demographic	Non-Metastatic (n=50)	Metastatic (n=42)
Age (Years): Median [Range]	66 [50-81]	73 [48-89]
Pathological Stage		
I	14 (28%)	0 (0%)
II	28 (56%)	0 (0%)
III	8 (16%)	0 (0%)
IV	0 (0%)	42 (100%)
Histology		
Adenocarcinoma	46 (92%)	39 (93%)
Neuroendocrine	0 (0%)	1 (2%)
Unknown	4 (8%)	2 (5%)
Gleason Score		
6	2 (4%)	2 (5%)
7	22 (44%)	14 (33%)
8	14 (28%)	7 (17%)
9	12 (24%)	15 (36%)
10	0 (0%)	1 (2%)
Unknown	0 (0%)	3 (7%)
Average PSA (ng/mL) [Median]	20.5 [7.1]	186.5 [30.3]
CAML Positivity # of Patients	38 (76%)	31 (74%)
Median CAMLs /7.5mL blood	3 [2]	6 [2]

MATERIALS & METHODS

We prospectively recruited (n=92) PC patients to examine CAMLs' in non-metastatic (stages I-III) and mPC; 15% (n=14/92) were stage I, 30% (n=28/92) stage II, 9% (n=8/92) stage III, & 46% (n=42/92) Stage IV. Blood was procured from Northwestern University, Fox Chase Cancer Center, Memorial Sloan Kettering Cancer Center, and Mayo Clinic according to local IRBs and written informed consent. Prior to induction of new therapy, or induction of first line therapy for newly diagnosed patients, 7.5mL peripheral blood was collected and filtered via CellSieve microfiltration. PSA was also monitored to compare prognostic significance against ≥50µm CAMLs and other circulating cells types. Univariate analysis was used to analyze progression free survival (PFS) and overall survival (OS).

Figure 3. Comparison of primary tumor circulating cell frequency among non-metastatic and metastatic PC patients



RESULTS

- CAMLs were found in 76% (n=69/90) of available samples, averaging ~3 CAMLs/7.5mL in non-metastatic and ~6 CAMLs/7.5mL in mPC patients
- CAML frequency was highest compared to other cancer circulating cells and independent of metastatic spread (**Fig. 3**)
- CAML size increased linearly with advancing disease (**Fig. 4**)
- ≥50µm CAMLs significantly predicted for poorer survival (**Fig. 5**)
- High PSA (≥50ng/mL) was a significant predictor for worse outcomes
- Changes in PSA throughout treatment was not a predictor

Figure 4. CAML size increased with advancing disease. (ANOVA) Stage I vs. IV p=0.007, Stage II vs. IV p=0.002, Stage III vs. IV p=0.693)

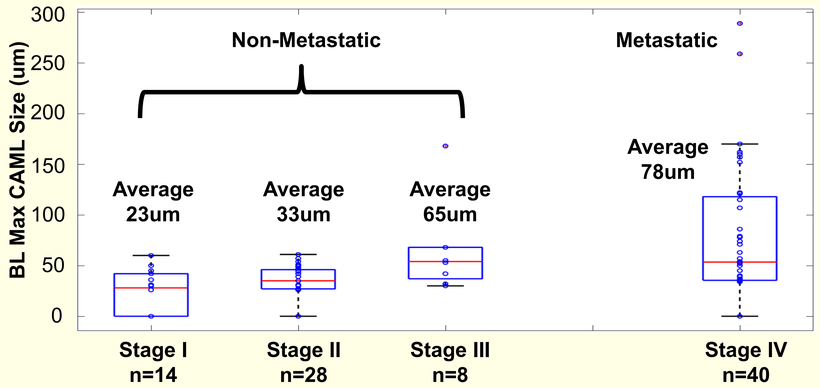
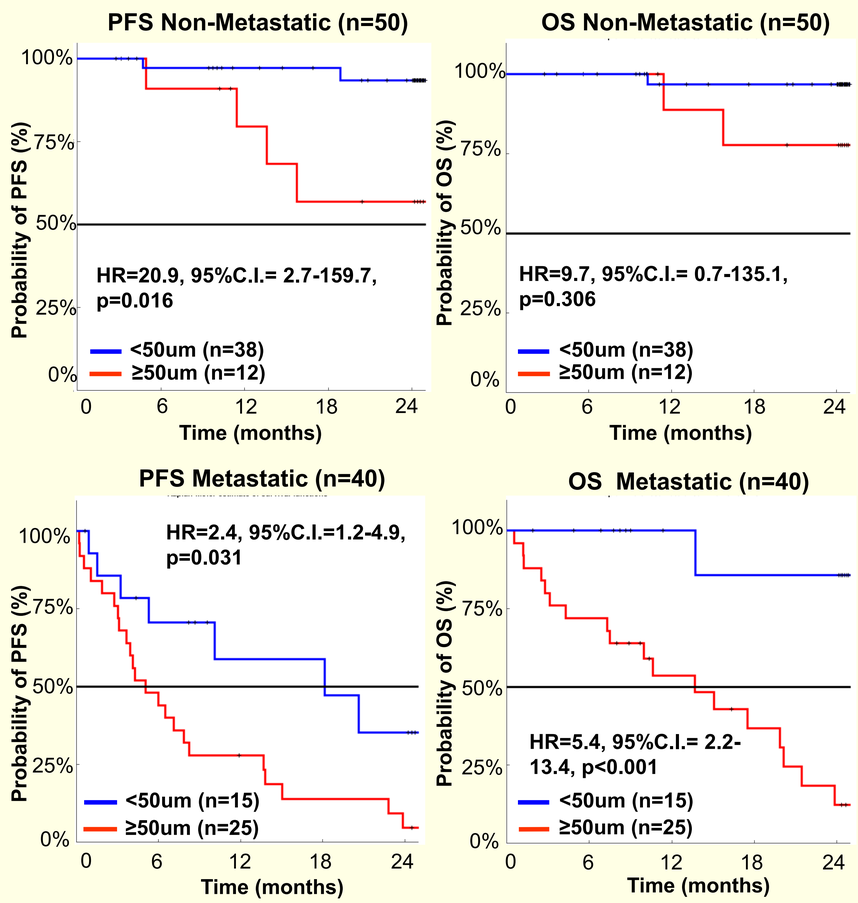


Figure 5. Kaplan-Meier of PFS and OS based on CAML Size



CONCLUSIONS

- CAMLs appear more frequent than other types of circulating cells (EMTs, CTCs) in both local and metastatic disease.
- ≥50µm CAMLs were highly significant, independent predictors of worsened survival compared to other clinical variables.
- ≥50µm CAML presence prior to induction of new therapies appears to detect highly aggressive PCs that may not respond to standard of care.
- Larger prospective validation cohorts on local and non-local disease should be established to validate these preliminary findings.

References

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